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by Ayly Soekanto

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Case Report

Neurological Abnormalities in Congenital Rubella Syndrome and Possible Pathophysiology

Erny[1)], Okky Prasetyo[2)], Ayli Soekanto[1)]

[1)]Medical Faculty, Wijayakusuma University, Surabaya
[2)]Department of Pediatrics, Faculty of Medicine,
Universitas Lambung Mangkurat, Banjarmasin

ABSTRACT

Background: Congenital rubella syndrome is a disease that is a relative severe health problem because it causes multiorgan disability. The purpose of the study was to describe the neurological abnormallities that occur in congenital rubella syndrome and its pathophysiology.
Case Presentation: A descriptive study with the subjects of the study of infants and children with congenital rubella syndrome found in the private practice of pediatricians for 10 years aged 1-5 years with the most complaints of developmental and growth delays, recurrent seizures and behavioral disorders. most are first children with mothers without Measles, Mumps, and Rubella (MMR) vaccination. Inclusion criteria: infants and children with clinical manifestations of at least 2 of all major clinical signs (hearing loss, congenital cataracts and congenital heart defects) accompanied by evidence of infection in the form of rubella-specific serum IgM and a history of the mother experiencing infection during pregnancy as evidenced by IgG results and or IgM rubella antibodies.
Results: 13 cases were obtained, 92.3% of the case population with multi-organ disability and only 1 case (7.69%) with neurological disorders alone. 84.6% of cases of neurological disability occurred as a result of infection in the 1st trimester.
Conclusion: Neurological abnormalities were acquired in the entire study population and were mostly due to infections in the 1st trimester of pregnancy.

Keywords: neurological abnormalities, congenital rubella syndrome.

Correspondence:
Erny. Pediatric Department Medical Faculty Wijayakusuma University. Jl. Dukuh Kupang XXV no 54 Surabaya, East Java, Indonesia. Email: drernyspa@gmail.com. Mobile: 0818-381-740.

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BACKGROUND

Congental rubella syndrome is multiorgan severe clinical manifestations due to exposure to rubella virus in pregnant woment in the period of organogenesis. The rubella virus in known to be highly contagious and has a teratogenic effect on fetuses with the manifestations of sedentary disability (Robertson et al., 2003).

Before the era of rubella vaccine administration in 1969, the incidence rate of congenital rubella syndrome globally ranged from 0.8-4/1000 live births and during the rubella epidemic 0.1-0.2/1000 live births (Anonymous, 2011). WHO estimates that 100,000 babies are infected with rubella every day worldwide. some studies for example in Fiji show a tendency to increase cases of congenital rubella syndrome from year to year. currently the majority of cases of congenital rubella syndrome occur in countries that have not included vasin rubella in the

country's national immunization program or there are still many people who have not independently carried out the vaccination even though the program already exists for various reasons (Efrén et al., 2015).

According to Pusdatin data from the Ministry of Health of the Republic of Indonesia in 2018, in the period 2010-2015 there were 30,463 rubella cases throughout Indonesia. However, the data does not mention in detail the type of rubella cases so the data on congental rubella syndrome nationally are not obtained (Kementerian Kesehatan RI Pusat Data dan Informasi, 2018). Research conducted (Herini et al., 2018) at Jogjakarta found a fairly high incidence rate of congenital rubella syndrome ranging from 0.05-1/1000 babies born alive. From Hasan Sadikin Hospital Bandung, 60 cases were found in 2018. Other research data from Fiji in 1995-2010 showed the incidence rate of congenital rubella syndrome ranged from 295 cases. Research from Bangladesh in 2011-2012 found 40 cases of congenital rubella syndrome (Nazme et al., 2014). The data mentioned above may be like an iceberg phenomenon because there are still many cases of rubella infection in pregnant women that are not diagnosed correctly due to relatively mild clinical symptoms.

The consequence of congenital rubella syndrome is that disability in infants is quite diverse ranging from defects in the eyes, heart, nerve systems, deafness, mental retardation and the other organ manifestations. This is permanently and have the great impacts in the baby's life in the future (Nazme et al., 2014). Neurological abnormalities due to congenital rubella syndrome are manifold. Most require corrective, rehabilitative action, special assistance and specific educational management according to the condition of each child's cognition and broadly speaking this is a considerable burden for the family, nation and state (Toizumi et al., 2017). This looks ironic considering that this condition should be prevented by giving vaccinations.

In 2011, WHO recommended that all countries that have not introduced the Rubella vaccine and have used 2 (two) doses of the Measles vaccine in the routine immunization program to include the Rubella vaccine in the routine immunization program. The National Immunization Expert Advisory Committee (ITAGI) also issued a recommendation on January 11, 2016 regarding the introduction, to integrate the Measles Rubella Vaccine (MR) into the national immunization program to reduce the incidence of Rubella and Congenital Rubella Syndrome diseases. All Rubella vaccines can cause seroconversion of 95% or more after administration of one dose of the vaccine and the efficacy of the vaccine is estimated to be around 90%-100%. Administration of 2 doses of the vaccine is stated to have a protective effect against rubella virus infection for longlife (Anonymous, 2011; Howard et al., 2020 Report, 2015).

The purpose of this study is to describe neurological abnormalities that occur due to congenital rubella syndrome and its pathophysiology.

CASE PRESENTATION

This research is description research with a cross-sectional approach of all suspected cases of congenital rubella syndrome that we met at the independent neuropediatrician clinic Jl Griya Kebraon Selatan FA 19 Surabaya from 2010 to 2020. The age of patients is between 1-5 years with the most major complaints of developmental and growth delays, recurrent seizures and behavioral complaint. The entire population is the first child and the history of pregnancy is considered normal by the parents. All mothers of patients have not been vaccinated with MMR and there is no history of similar illness in

the family. laboratory examination of anti-rubella IgG and IgM in mothers is carried out as a screening during the I and II trimester of pregnancy even without maternal clinical manifestations.

Inclusion criteria are babies and children with 2 or more from main clinical manifestation from congental rubella syndrome (deafness, congenital cataract, congental heart disease), neurology abnormalities and evidence of rubella virus infection in the form of rubella-specific serum IgM and a history of the mother having rubella virus infection during pregnancy as evidenced by IgG examination and or rubella antibody IgM.

RESULTS

During the 10 years from 2010-2020 we encountered 13 cases of congenital rubella syndrome with various neurological manifestations and other manifestations which consists of congenital cataract, congenital heart disease, deafness.

The results showed population consists of boys 61.5% and girls 38.4%. Rubella virus infection 84.6% occurs in the first trimester and 15.4% occurs in the second trimester. Clinical manifestations consist of neurological abnormalities (100%), congenital heart defects (84.6%), congenital cataract (69.2%), deafness (61.5%) and growth retardation (61.5%). In most of the study population found multiple clinical manifestations.

The clinical manifestations of neurology vary widely, mental retardation (100%) with varying degrees ranging from mild mental retardation to idiots. The next most common manifestations are lethargy, hypotonia, behavioral disorders, seizures and motor delay. Other clinical manifestations are hydrocephalus, meningitis, panencephalitis, and autistics. Such manifestations can be found in combination in one patient.

Table 1. Characteristics Sample

Characteristic	Categories	Frequency (n)	Percentage (%)
Gender	Male	8	61.5%
	Female	5	38.4%
Trimester	I	11	84.6%
	II	2	15.4%
CHD	Yes	11	84.6%
	No	2	15.4%
Conginetal Cataract	Yes	9	84.6%
	No	4	15.4%
Deafness	Yes	8	(61.5%)
	No	5	38.5%
Neurological Abnormalities	Yes	13	(100%)
	No	0	0%
Growth Retardation	Yes	8	61.5%
	No	5	38.5%

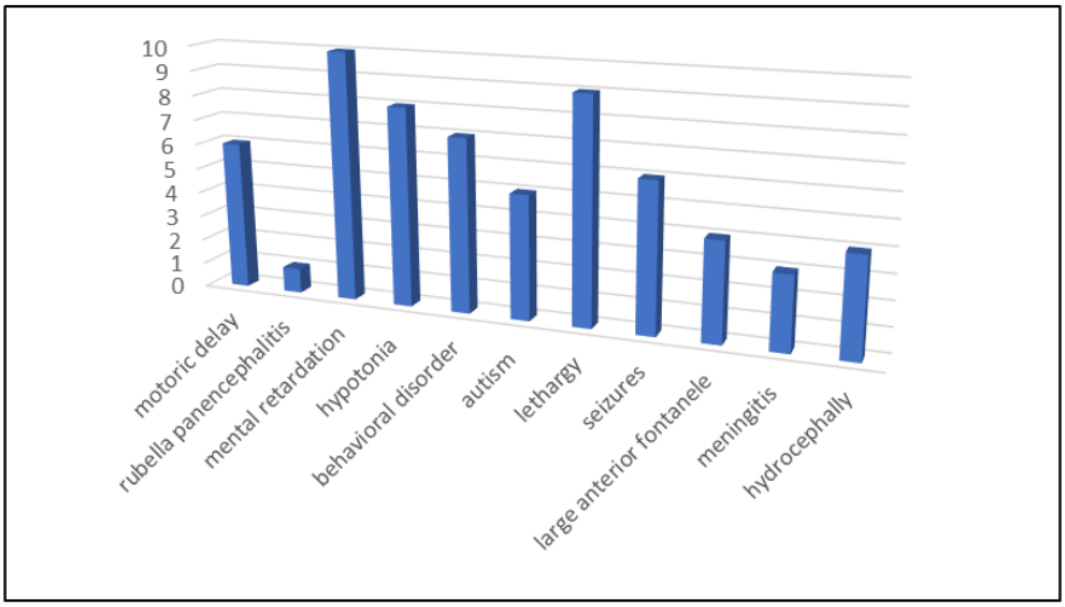

Figure 1. Neurological manifestations of Congenital Rubella Syndrome

DISCUSSION

Rubella virus (RUBV) is the only member of the genus Rubivirus in the family Togaviridae (Mangala Prasad et al., 2017; Nazme et al., 2014). This virus is classified as a virus that has a ribonucleic acid genome that is able to replicate in the cytoplasm of host cells but does not integrate into the host genome. The life cycle of RUBV begins with the process of viral adhesion to the host cell through the glycoprotein oligodendrocyte myelin receptor which can occur rapidly ranging from 30 minutes to 3 hours after exposure to infection (Adamo et al., 2008; Cong et al., 2011). The structural components of the virus consist of 3 proteins, glycoproteins E1, E2 and capsid proteins play a very important role in the process of attachment to the host cell receptor, membrane fusion and viral transport in the cellular compartment and are ultimately an important part in the pathogenesis of the disease (Cong et al., 2011; George et al., 2019; Mangala Prasad et al., 2017).

Congenital rubella syndrome was introduced by South and Sever with reference to conditions of complications or disability in the fetus due to exposure to rubella virus infection in early trimester pregnant women (Lee & Bowden, 2000; Mawson & Croft, 2019a) Nguyen et al., 2015). The probability of infection in the fetus depends largely on the time of infection of the pregnant woman, if the rubella virus infection occurs in the 1st trimester the probability of the fetus having infection is about 80% and this prevalence decreases along with an increase in gestational age (Lee & Bowden, 2000; Xu, 2013). The hypothesis presented in this regard is the ability of pregnant women to increase the production of linear-specific IgG antibodies with increasing gestational age which are subsequently transferred to the fetus through placenta. In this study, it was proven that 84.6% of cases of severe neurological disability occurred due to rubella virus infection in the 1st trimester.

Rubella infection in early trimester pregnant women to date has a strong potential in inducing various fetal defects, especially in the CNS for example microcephaly, mental retardation, encephalitis, cerebral palsy, autism, schizophrenia and sensorineural deafness (Efrén et al.,2015; Herini et al., 2018). Congenital rubella syndrome having clinical picture in the form of reduced organ size and due to angiopathy in placental tissues at initial phase of embryonic development (Garcia et al., 2016; Lee & Bowden, 2000). This study showed that 92.3% of the case population had multi-organ disability and mostly infection occured in the 1st trimester and only 1 case with neurological abnormalities and the case was rubella virus infection occurred in the 2nd trimester.

Microscopic analysis of RUBV-infected fetuses showed cellular damage in some places, with non-inflammatory necrosis mainly in the eyes, heart, brain, and ear (Garcia et al., 2016; Lee and Bowden, 2000; Toizumi et al., 2017; Xu, 2013). The most prominent abnormalities are vascular abnormalities consisting of focal destruction of blood vessels, internal defects of the lamina elastica, deposition of granulary matter and endothelial proliferation, decrease in the thickness of cerebri cortex tissue with dilatation of the ventricles of the brain and necrosis of the white matter of the brain with a decrease in the number of oligodendrocyte cells (Cong et al., 2011; Mawson & Croft, 2019).

Many mechanisms have been proposed as hypotheses regarding the ability of rubella virus to induce all such damage. From some experimental studies it is known that there is a disturbance of the balance of the process of nerve cell proliferation and differentiation that has a great impact on organogenesis through several mechanisms consisting of rubella virus infection is able to trigger an increase in the process of apoptosis and the occurrence of necrosis of nerve cells especially oligodendrocytes, astrocytes and if the infection occurs in the first trimester which is also the phase of organogenesis (Cong et al., 2011), the virus will induce damage to progenitor cells that stop the cell cycle so that there is a slowdown in cell division which ultimately leads to fetal growth retardation (Adamo et al., 2008). This hypothesis supports the onset of clinical symptoms of microcephaly and psychiatric disorders e.g.schizophrenia in congenital rubella syndrome (Brown, 2011). The hypothesis also relates to the results of the disruption of brain maturation programs in the prenatal phase and the neonatal phase. In addition to this, severe neurological abnormalities are also thought to be caused by vascular damage that occurs as part of the pathogenesis of congenital rubella syndrome.

In addition to the direct effect of rubella virus infection on host tissues, there is the fact that damage to babies with congenital rubella syndrome still persists until the perinatal period is thought to be mediated by the baby's own immune system. In in vitro studies, it appears that rubella virus infection is an IFN inducer which although on a low scale when compared to other teratogen viruses but IFN is detected in high concentrations in the placenta in the midgestation phase (Sakuragi et al., 2022). Several studies have found the fact of cytokine storms in congenital rubella syndrome that cause a lot of multiorgan damage as evidenced by the findings of an immune system complex containing rubella virus antigens in systemically circulating serum (Frenkel et al., 2018; Sakuragi et al., 2022; Shukla & Maraqa, 2022). Cytologically, mononuclear inflamatoric infiltrates were found in several organs of the body of babies who died, especially in the brain and lungs (Kumar et al., 2022). In

addition, advanced clinical manifestations in congenital rubella syndrome are also thought to be mediated by an immune response (Lee and Bowden, 2000).

In this study, children born with congenital rubella syndrome mostly infected in the first trimester of pregnancy. Severe clinical manifestations of neurology were found in the entire study population with the most clinical manifestations in the form of mental retardation and motor abnormalities. From various literatures, the hypotheses presented in connection with the pathophysiology of the occurrence of disability in neurology are placenta angiopathy, necrosis of the white part of the cerebral cortex and increasing apoptosis and damage to oligodendrocyte and astrocyte cells. In addition, cytokine storms were also found that continued in the post-natal period and caused a lot of multiorgan damage.

AUTHOR CONTRIBUTION

Erny research population finder, establish a diagnosis and conduct an analysis, final writing of the study. Okky prasetyo looking for references and conducting analysis by case se ayli Soekanto earch for references and perform analysis by case

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CONFLICT OF INTEREST

There are no conflicts of interest.

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